THE MÜTTER LECTURES ON SELECTED TOPICS IN SURGICAL PATHOLOGY.

SERIES OF 1890-1.[1]

By ROSWELL PARK, A.M., M.D.,

OF BUFFALO,

PROFESSOR OF SURGERY, MEDICAL DEPARTMENT, UNIVERSITY OF BUFFALO; SURGEON TO THE BUFFALO GENERAL HOSPITAL, ETC.

LECTURE VII.

SURGICAL DISEASES OF MICROBIC ORIGIN.

SYLLABUS.—*Actinomycosis:* History. Description of the disease, and of the fungus. Actinomycosis in man. Paths of infection.

Anthrax: History. Sources of infection. Bacillus anthracis; its characteristics; intensification and diminution of its virulence.

Malignant Œdema: Gangrenous emphysema. Description of the disease. Anatomical characteristics. Description of its bacillus; biological peculiarities. Immunity enjoyed by certain animals.

Rauschbrand: Symptomatic anthrax. Strong resemblance to malignant œdema; essential differences. Description of its bacilli.

Glanders or Farcy: Brief reference to its infectious organism; the bacillus mallei. Difficulties of diagnosis.

ACTINOMYCOSIS.

UNDER one name or another the peculiar manifestations now known to be the result of the condition termed actinomycosis have been recognized in nearly all civilized countries, and have been noticed especially about the head and neck of domestic animals, particularly cattle. The large variety of names given to these lesions constitutes the best indication of the fact that their etiology was unknown. During the past thirty or forty years they have been more and more carefully studied by veterinarians. In England, for instance, as early as 1833 a peculiar swelling met with in cattle, and known locally as *clyers*, had been somewhat carefully studied by Professor Dick. He dissected several animals which presented these tumors in the parts about the throat, and described them as having a somewhat malignant character, and corresponding to what were usually called "medullary carcinomatous tumors." He noticed also that sometimes abscesses developed, and that when these were laid open healing frequently followed, and that in other cases the open sores remained indolent for a time and then increased until they interrupted respiration by their bulk, and prevented deglutition. In 1841 he made a further report on the same subject, describing now the mouth and throat of a cow in which there was a distinctive tumor, and he spoke of it as a mass of fungus flesh, while a part of the jaw was decayed and absorbed. This time he stated that the disease was not unknown in cattle and that it was well-known as attacking the jaws in human beings; that by surgeons it was denominated osteo-sarcoma of the maxillary bones, and he added that the remote cause seemed to be a scrofulous diathesis, while the existing cause was commonly disease of the molar teeth, or some accidental injury. In 1843 a Mr. Relph described in *The Veterinarian* a "kind of indurated tumor" which he met with in his practice oftener than anything except the common wens. He spoke also of its ulceration and extension until at length animals sank and died of "atrophy or phthisis pulmonarius." He spoke also of a section of one of these tumors as "mostly displaying several abscesses with matter varying in consistency, and often very fetid, enclosed in what seemed to be fibro-cartilaginous cysts." Also, again, of the implication of the nasal sinuses and involvement of the orbital cavity, where bone was being removed and matter deposited, and also that the tongue was much enlarged and ulcerated. In 1845 Professor Simmonds spoke of the diseased condition as an affection termed *scirrhus tongue*, and one frequently found associated with maladies essentially different. Under this term, scirrhus tongue, it was commonly described until quite recently. In 1864 a case was fully described in the *Ed. Vet. Rev.* under the title of "Cancer of the Tongue in an Ox." On the continent also this disease had been everywhere misunderstood. It had been frequently regarded as a tubercular infection or mistaken for a simple chronic glossitis; while the continental languages were full of common names for it, and veterinarians spoke of it as osteo-sarcoma, bone cancer, spina ventosa, etc. In 1876 Bollinger presented to the Society for Morphology and Philosophy at Munich a learned paper on the subject, with a demonstration of microscopical and gross specimens. He pointed out that these tumors consisted of several centres of growth bound together by connective tissue, whose cut surfaces presented yellowish white suppurative foci, or at times a spongy texture, owing to the formation of minute cavities in a fibrinous crust, which contained a thick, yellow, caseous pulp. The microscope revealed a structure something like that of sarcoma, while the expressed juice contained, among other materials, small granular bodies which had a mulberry like appearance, and were sometimes encrusted with chalky matter. He had discovered that these latter bodies were true fungi, and he further maintained from the constancy of their appearance and they were not accidental but had a pathological significance. These also he had met with in old museum specimens.

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[1] Delivered before the College of Physicians, Philadelphia, December, 1890.

Bollinger had observed this remarkable formation not only in the upper and lower jaws, but also in the tongue, in which latter organ, when recent, it much resembled the condition produced by tuberculosis. If these nodules were situated on the surface of the tongue they rapidly led to the formation of ulcers. It was possible also for an interstitial glossitis to occur, which, in spite of partial atrophy of muscle fibres, led to enlargement and peculiar hardness of the tongue, from which the infection gained, in German, its popular name *holz-zunge*, or wooden-tongue. On continuing his researches further, he discovered the same fungus in tumors which occurred in the pharynx, larynx and stomach. He even described this fungus in a case of so-called fibroid of the second stomach of a cow, and in a form of apparent tubercular ulceration of the intestines. He submitted the fungus to the botanist Harz, who described it and assigned it to a temporary position. Cultivation experiments and inoculation of the tongue of a calf with liquid containing the organism, all failed. Its name was given by Harz. Bollinger's paper was published in 1877 and attracted wide-spread attention, and brought out the claim from Perroncito and Rivolta that they had already discovered the same organism in 1863 and 1868 respectively. It is very probable that Hahn, of Munich, met with the fungus in 1870, since he states that in a case of wooden-tongue he found characteristic structures, which he described provisionally as a species of mould fungus, but Bollinger was certainly the first to study the organism systematically, and to throw an entirely new light upon the pathology of the infection, and his researches were corroborated by Siedamgrotzky, by Johne and by Ponfick; and so by one observer and another on the continent, and later in Great Britain, the pathological identity of the various lesions included under so many different names was established, and the names of Boström and Israel, of Axe and Crookshank, and of many others in addition to those already named, have become inseparable from the subject itself. During the year 1858 a most important memoir was sent to the agricultural department of the Privy Council by Professor Crookshank, of King's College, which was published in the annual report of that department for that year. It is a most elaborate document, extensively illustrated, and prepared with the greatest care, and to it the writer is largely indebted. One of the things for which we are especially indebted to Professor Crookshank in this matter is the establishment of the fact that many of the lesions in animals which had before been considered due to tuberculosis, are in reality manifestations of actinomycotic disease, a beautiful proof of which that gentleman has kindly afforded me in his own laboratory, while in the document referred to it is amply evidenced by illustration. Altogether we regard this report pertaining to animals and men as well, and comprising 80 pages, as presenting perhaps the best summary of the subject which we have.

The disease, as Crookshank and others succinctly state, belongs to the class of infective granulomata. It has an irritative, inflammatory action, brought about by the presence of a special irritant, a microphyte, and consists of a collection of round, epitheloid, lymphoid and giant cells, enclosed within a fibrous reticulum. There are thus constituted nodular tumors of various sizes. Sometimes these attain large dimensions, at other times they break down early and suppurate. While it appears, as seen in a former lecture, that the actinomycotic fungus may by itself produce pus, it is nevertheless equally true that suppuration in actinomycotic tumors is commonly due to a secondary infection by the ordinary pyogenic organisms. Calcification takes place sometimes in the fungus tufts, and altogether the actinomycotic nodule so closely resembles the tubercular in its minute character that it constitutes almost a mimicry of the latter. Its most characteristic manifestation in cattle is betokened by the popular name most frequently given to it, namely, *lumpy jaw*. It is especially prevalent in river valleys and marshes, and on land reclaimed from the sea, and in animals appears to occur more frequently in the winter, and more often in the young than in the old. There is strong reason for believing that the fungus gains access to the system through wounds or ulceration of the mucous membrane, or through carious tissue. It has been pointed out that the common occurrence of the disease at the time of second dentition may be due to the wounds produced during the shedding of the teeth. It is supposed, also, that thistles and frozen roots, by wounding the parts, may afford a path of entrance. Discharges from infected animals are thus infectious, and cow sheds and pastures, drinking troughs and fodder may be easily contaminated.

The fungus itself may be detected with the naked eye in the discharge of an actinomycotic ulcer, or in the scraping from a cut surface or growth. Its tufts vary in size from that of a grain of sand to that of a pin's head. If the material contained be spread out on a slide and examined against a dark back-ground, these granules appear white or yellow-white in color, but if examined in transmitted light they appear distinctly brownish. If they are pressed down with a cover-glass they readily flatten out, while possibly a distinct gritty sensation is transmitted to the finger, owing to the presence of calcareous matter. With a low power the fungus will be recognized in the form of irregular patches scattered over the field, which might at first be mistaken for granular debris, but which on more exact examination will be observed to have a characteristic appearance. With a higher power masses will be seen which look like a rosette of clubs, or which have here and there throughout the margin a club-shaped projection. Of course with these bodies, pus cells and other granules will be found. By pressing upon the cover the rosette is broken up and then the club forms are recognized singly or in twos, or in the shape of fan-shaped segments. The presence of calcium salts may be readily demonstrated by the acids which dissolve them; by which the clubs are not affected. The club-shaped masses are not affected by ether, nor by potassium hydrate, which shows that they are not fat crystals. By teasing the little cluster we may break it up into its club like elements, and these may be examined with still higher powers. When these grains are placed in water and teased out, the center portion seems to be composed of a structureless core. When the organism is removed from the disease in man, it appears to present minute and delicate filaments which are not present in those removed from animals.

Actinomyces were generally regarded as belonging to the higher micro-fungi until Boström put forward a new theory. By Harz and Johne the club-shaped prolongations were considered to be conidia and the threads to be hyphæ. Boström on the other hand thought that the clubs should not be regarded as conidia, but the result of a pathological stage of the threads, and he considered that the calcification which occurs in them supports his view. If this were the case, cultivations could not be successfully made from the clubs, but must be made from fungi containing threads. He made cultures from five animal cases and one human, and obtained a similar result from all. The fungi were isolated from pus with sterilized needles, were placed in liquified gelatine, in which they were teased out, and the gelatine then spread on glass plates. In a few days the growth became visible. The fungi were then isolated from the plates, crushed between sterilized glass slides, and planted on the surface of nutrient agar and blood serum. In this way pure cultivations were obtained, and the culture which I show you herewith is made from a descendant of one of his original cultures. It grows in a peculiar way, with a finely granular whitish appearance; after a few days small yellowish red spots appear in the center, increase in size for a week or so, and then become confluent, while the margin is also dotted with similar spots. Isolated colonies as they appear have a yellowish red center with a grayish margin. Boström states that the actinomycis is not one of the mould fungi, and its central threads do not constitute a mycelium. He was inclined to regard it as a branched cladothrix.

Johne and Ponfick made a careful series of experiments to prove that actinomycosis is transmissible from animal to animal. Inoculation experiments, whether subcutaneous or intraperitoneal, as well as intra-veinous injection, were successful. Feeding experiments gave negative results. It appears from their researches that rabbits and dogs possess a marked immunity, while the cow is, perhaps, the most susceptible of all animals.

We are naturally most interested in this disease as it appears in man. In 1878 Israel published the drawings made in 1845 by Langenbeck, then in Kiel, of a case of vertebral caries, in the pus from which peculiar bodies were observed. There can be but little doubt that these structures were the fungi of actinomycosis. But the first published observations will be found in Lebert's large work on pathological anatomy, described in the text and figured in the atlas. In 1848 Lebert received some pus of great consistency which had been obtained from an abscess in the thoracic wall in an elderly man. The patient had been thought to have a cancerous pulmonary affection. The pus contained a very considerable quantity of minute spherical beads, which could be crushed between two strips of glass, and in which, under a low power, radiating wedge-shaped bodies were found. Lebert tested these bodies most carefully with chemical reagents, and had in mind the possible existence of some helminthic débris of which these bodies might be hooklets, but he sought in vain for the common parasites. Actinomycotic pus was later described and figured by Robin, but the first adequate description of the disease in man was made by Israel, who was soon followed by

Ponfick. By these two writers the various cases which had been observed up to that date were collected and described and the disease classified according to the seat of invasion. Up to the time of Crookshank's report he had collected about one hundred and thirty human cases, and from those as well as from the work of Israel, the following description is largely drawn.

Invasion by the mouth and pharynx.—The fungus may gain access through carious teeth or wounds or fistulæ of the jaw, and possibly by the pharynx and tonsils; it attacks the lower jaw most frequently. The consequent tumor is found in close connection with the bone, and just beneath the jaw or in front of the trachea. Actinomycotic tumors in this region appear to correspond very closely with the *clyers* already described in cattle. As in cattle, they may discharge through the skin, although they differ in their tendency to form burrowing abscesses instead of recognizable tumors. The upper jaw is much less frequently attacked than the lower. The progress of the disease is usually slow, and there is a tendency to the deep seated parts becoming involved; while when the lower jaw is attacked the tumors tend to approach the surface. In other cases the disease has been described as extending from the alveolar process to the temporal bone or the base of the skull, destroying these bones and even reaching the brain. In yet other cases, it has extended along the spinal column, implicating the vertebræ and traveling and pointing in various directions. The first cases of actinomycosis hominis which were observed in this country were connected with the jaw, and were described by Dr. Murphy, of Chicago. Both recovered after thorough curetting. In one recorded case the disease existed for seven years, was localized in the bronchi (bronchitis actinomycotica) and did not extend into the lungs. The sputum was examined and contained the characteristic fungus. If the fungi be inhaled they pass into the lungs and produce proliferation of round cells, which undergo fatty degeneration. The resulting patches of peri-bronchitis or pneumonia become yellowish white. Suppuration and hæmorrhage follow, and the resulting small cavities contain pus cells, fat granules, blood and fungi; ultimately a dense layer of connective tissue is formed around the cavities, which are lined with granulation tissue containing the characteristic fungus. The symptoms are usually obscure, but the specific organism may be found in the sputum, and is in fact often recognizable with the naked eye. The apices of the lungs are not, as a rule, affected. There is considerable resemblance in clinical course to chronic or fibroid phthisis. In the second stage the symptoms are more severe. The disease spreads to neighboring parts and often pleurisy supervenes. The disease has been known to descend behind the diaphragm and point as a psoas or lumbar abscess; or to perforate the diaphragm, reach the abdominal cavity, and there set up peritonitis or sub-phrenic abscess. The disease may also extend forward in the direction of the pericardium and anterior mediastinum. In the third stage the disease comes to the surface, either over the chest or in the neighborhood of the vertebræ; a livid swelling appears from which no fluid escapes on puncture, but which works its way to the surface, and then discharges the muco-purulent fluid, in which the fungi are easily recognized.

Invasion by the digestive tract.—Chiari has published a case dying from general marasmus, after two years' illness, at the age of 34. The mucous membrane of the intestines was completely covered with whitish patches closely adherent to the adjacent tissues. In this case the teeth were carious. In such cases generally small nodules about the size of a pea may be found in the sub-mucous tissue and in the mucosa itself, they soften and form ulcers with determined edges, their bases reaching the deepest layer. These may undergo cicatrization, but generally ulceration extends through the peritoneum to the abdominal cavity, and we have perforation of the bladder or the intestines, or perhaps of the abdominal wall. Symptoms are absent or not characteristic. The fungus may be found in the evacuations or by exploratory puncture.

Besides such cases as the above, which can be easily classified, there are a number of recorded cases presenting varied symptoms and anatomical relations in which the path of infection has not been determined. It may be said in common of all cases, however, that no matter where the lesions may be situated, the discharges therefrom present always typical characteristics.

The first case of actinomycosis in man met with in Great Britain was described by Dr. Harley in 1885, the patient being an inmate of St. Thomas Hospital. The next two cases were recognized by Mr. Shattock, who published them in the "Pathological Transactions" in 1884 and 1885. Numerous other cases are described in English journals, and it is a matter of interest to know that numerous specimens which had long been deposited in museums, that of the College of Surgeons, for instance, and had been described under other names, were found to be genuine cases of actinomycosis. It is worth while also to know that since the introduction of Gram's method of staining, a distinctive advance in the recognition of the organism has been made, since by this method, combined with staining by orange rubin, as pointed out by Crookshank, the threads are stained blue and the clubs crimson, while in the younger clubs the protoplasm of the thread can be traced into their interior. Evidently, then, the best method of preparation is Gram's stain followed by eosin or orange rubin. Inasmuch as Gram's method had not been applied by either Israel or Koch in the earlier part of their studies of this disease, it is not strange that most of their writings have failed in the complete description of the organism which the later reporters have given.

So far as the source of the disease in man is known, many interesting observations have been made. Two cases have been recorded in support of a theory of direct infection from the cow. One of these occurred in a man who had the care of animals, some of which were diseased, the other in a man who had charge of cows, one of which had a tumor of the jaw, which tumor he had opened. On the other hand Moosbrugger found that out of seventy-five cases, fifty-four were in men, nineteen in women and two in young girls. In eleven of these the occupation was not stated, in thirty-three their occupations did not bring them into contact with diseased animals. Only ten of his cases occurred among farmers, peasants and farm laborers, and only one of these ten had been brought into contact with diseased animals. Of the twenty-one women there were only four peasants and none of them had been taking care of diseased animals. Infection by the flesh of diseased animals has also been discussed, but there is no evidence of prevalence of the disease among butchers, who would be particularly liable to it if flesh were a source of infection. Moreover the chances of infection from this source are minimized by the flesh being almost always cooked. To be sure the disease occurs also in pigs, and pork is often eaten in an uncooked state; and Israel has pointed out that the disease has never been known to occur among strict Jews. Evidence seems to point to the origin of the disease among the cereal foods. This view is supported by observations with reference to the part played by cereals in inducing the disease in cattle, an origin well known, and it gains additional support from a case described by Soltman where the disease resulted from swallowing an awn of barley. This was accidentally swallowed by a boy of 11, who became very ill and suffered great pain behind the sternum extending to the back. An abscess formed, covering an area extending over this inter-costal space, and when opened the awn of barley was found in the evacuated pus, but pain continued and fresh deposits occurred, and when the boy was taken to the hospital, the specific fungus was detected.

As Crookshank states, it has not been possible to trace every step in the life history of many of the basidiomycetes; but if we regard the ray fungus in the light of what is known to occur in many species, this life history may be explained about as he explains it, thus: The spores sprout into hyphæ, and these form fine threads which branch irregularly and sometimes dichotomously; the extremities of the branches develope the club-shaped bodies; these are so closely packed together that a more or less globular body is formed with a central core composed of a dense mycelium. By Gram's method, these threads can be differentiated into an external sheath with protoplasmic contents. The club-shaped body appears to be externally mucilaginous, while internally it is continuous with the protoplasm of the thread. In all probability the clubs represent organisms of fructification. If this be correct the protoplasm in the interior of the club may possibly undergo changes leading to spore formation, the spores being ultimately set free. At other times the clubs themselves seem to sprout, and the sprouting forms to suggest teleuto-spores. In whatever way formed, there is but little doubt that spores are set free in the vicinity of a rosette, and give rise to fresh individuals, and that spores and young fungi are taken up by wandering cells, by which they are conveyed to a distance where they reproduce their kind.

At the Congress of German Surgeons in 1890, Israel and Wolff made an important communication on ray fungi, and their successful cultivation outside of the animal organism, and their successful implantation of such cultures upon the animal. In this a claim was made that they were the first to succeed in cultivating the actinomycosis and implanting it, which claim would appear to be unjustifiable, since, so far as I can learn, Boström anticipated them in this work by several years. Still their remarks and their demonstrations were most entertaining, and the question of priority is one of minor importance. That they did succeed is established, and the fact that it is possible to produce an artificial actinomycotic disease in animals is established beyond a doubt.

ANTHRAX.

This goes also by the name of *milzbrand* in German, *charbon* in French, and is known in common parlance as *malignant pustule*, *woolsorter's disease*, and often as *carbuncle*. The latter, term however, is unfortunate and is liable to misuse. The common carbuncle is simply a phlegmonous process accompanied with a large amount of tissue necrosis, produced probably by common pyogenic or perhaps saprogenic forms, and although I have once found in the blood taken from a large typical carbuncle of this character, on the back of the neck, bacilli much resembling in form and appearance those of true anthrax, I regard their presence there as accidental and do not think that I had to deal with any specific form. On the other hand the malignant pustule of animals has about it much that reminds one of carbuncle in man. In animals the disease has been known for centuries, although it remained for observers who are still living to demonstrate the specific organism by which it produces contagion. Various descriptions of the disease in man occurred during the latter part of the previous century, and its primary existence in man was apparently first claimed by Boyle in 1800.

Of the specific bacillus which is the prime cause of this disease it is hardly necessary to speak, except to remind you of its peculiar resistibility to influences which are destructive to most micro-organisms, and of the little trouble with which it can be utilized in the laboratory because it is so easily cultivated, so readily inoculated and because of the ease with which it can be demonstrated in the circulation and the tissues. In scarcely any organism can the development of spores be better watched, and except for the dangers attending carelessness in handling, it is a most satisfactory organism with which to work. There is this peculiarity attending it, that in the bodies of living animals these organisms multiply solely by segmentation, never producing spores while their host is still alive. Their spores are produced only in dead media, with favoring temperature, whose limits are 15 and 45C. According to Koch, the disease spreads among animals by germinating spores which cling to grasses and plants in moist localities, and which are taken in with the food and cause the intestines to become the first seat of infection.

When the disease occurs in man it is almost invariably contracted from the carcass of some infected animal, or the products of the same. The term wool sorter's disease is most significant, as showing, perhaps, the most common source of contagion. So long as the skin remains intact it is protected; the slightest abrasion may serve as port of entry for the germs; even the mucous membranes may be infected either by bacilli or their spores. It is said that these latter are so minute that they may reach the circulation through a healthy mucous membrane; and the disease is often conveyed by the bites of mosquitoes or flies which have fed on infected animals.

The micro-organism of anthrax has been studied more than any other save that of tubercle, and some remarkable effects have been produced by experiments with it in the direction both of intensification and attenuation. By cultivating it in bouillon for three weeks its infectious power is diminished, and animals inoculated with it are in large measure protected against the disease. Still further immunity is obtained by a second inoculation with material not quite so weak. Animals thus treated a second time are protected for some time against the most virulent form of the disease. Woolbridge secured immunity by cultivating the bacillus in an alkaline solution at blood temperature for two days; he then filtered the fluid and injected a small quantity of it into the subcutaneous tissue of rabbits, which remained well and resisted injection of most virulent blood. Some of Koch's pupils have isolated an albuminose from anthrax cultures, which renders small animals immune against the most virulent cultures. This was prepared by a precipitation with absolute alcohol, and was separated from all possible ptomaines by the same medium. It was then redissolved and filtered through the Chamberland filter. Animals which were inoculated with virulent anthrax spores and injected at the same time with this albuminose recovered. Ten mice each received one-millionth of their body weight of anthrax albuminose, and anthrax culture at the same time. Of these only three died. Vaccination after this fashion has been carried on extensively, among sheep, by Pasteur and his pupils or assistants, and a large degree of success has been attained, although by no means all the animals have survived; and the spread of the disease in France has thus been largely checked.

On the other hand the virulence of the bacillus is increased by successive inoculations in susceptible animals, although it is decreased by passing through different species of animals. It has also been found that attenuated virus will become more virulent by adding certain substances, for instance, a very small proportion of lactic acid; one five-hundredth part of this acid, added to a mixture and allowed to stand for twenty-four hours, doubles its virulence. If to this mixture a little fermentescible sugar is added, in another day the virulence becomes extreme, and frogs, which inoculated with ordinary virus live from forty to fifty hours, when vaccinated with this intensified material die in from twelve to fifteen.

When the spores of anthrax are inhaled, we have primary bronchial and pulmonary lesions. When ingested with infected food or water, we have primary intestinal anthrax. Secondary specific bronchitis, pneumonia or enteritis are met with in almost all cases, if time enough elapse. When the spores are inhaled they lodge upon the mucous membrane, are quickly converted into bacilli, and then insinuate themselves between the cells and into the capillary vessels. In the intestine they affect the mesenteric side of the bowel, lodging usually upon the more prominent ridges of mucous membrane.

Bollinger classified lesions in man as follows:

1. Anthrax acutissimus or apoplectiformis.
2. Anthrax acutis.
3. Anthrax sub-acutis.

External infection is usually produced through a small wound or abrasion. If the microbe meets with sufficient resistance at the point of invasion, its activity is largely or entirely localized; if not, it enters the blood-vessels, causes general and fatal infection. The so-called malignant pustule is in large measure determined by anatomical structure, which needs be dense and vascular. This quickly forms a phlegmonous necrotic area, resembling in most respects a common carbuncle. If, however, a vein be opened in the infectious process, general infection is not prevented by formation of thrombi. There is another form of this disease known as *anthrax œdema* which occurs in parts composed of loose connective tissue with meagre blood supply, conditions met with about the eyelids and neck. Here the disease appears as a flat infiltration without well-defined borders, the skin being little or not at all discolored, while an œdema spreads rapidly in all directions. General infection occurs more easily from this form than from the other, although spontaneous cure is possible. So long as infection remains local, there are few general symptoms; but with general infection we have signs of rapid and overwhelming sepsis.

In man this inflammation seldom terminates in suppuration without secondary infection by pyogenic cocci, which, however, may easily occur. Bollinger believes that in his first and most virulent form the rapid growth of the bacillus in the vessels brings about a sudden diminution of oxygen, and a surplus of carbonic di-oxide with consequent asphyxia; but experiments fail to confirm this view. Another hypothesis is that death results from mechanical causes, that is, obstruction in the blood vessels from large numbers of bacilli; but this is not borne out by facts. The view that the essential toxic agent is some chemical substance generated by the bacilli has much more to commend it. Bollinger and others have succeeded in separating from anthrax cultures an alkaline substance or alkaloid having profoundly toxic effects, and, without rehearsing the various experiments which have been made, there is every reason to believe that the fatal termination from anthrax is largely due to the action of toxic ptomaines or of toxines produced by the bacilli as products of their growth.

Woodhead and Wood have experimented with a combination of anthrax and bacillus pyocyaneus, and they have found that anthrax bacilli which would kill a control animal in three days required nearly three times as long when twice a day a sterilized pyocyaneus culture was injected underneath the skin. They are of the opinion that this effect is not produced through phagocytosis, but through an antagonism of poison, since outside of a body the anthrax bacillus grows very well in a culture of green pus.

MALIGNANT ŒDEMA.

The disease known as malignant œdema, to whose parasitic nature especially I desire now to call attention, has been recognized for some time under such names as *gangrène foudroyante* (Maisonneuve), *gangrène gazeuse, acute purulent œdema* (Pirogoff), *septicémie suraiguë and septicemie gangrèneuse;* also as *gangrenous emphysema.* The term under which we speak of it, namely, malignant œdema, was given it by Koch, who identified its parasite. It is one of the most dangerous forms of gangrenous inflammation, which occurs sometimes after serious bone injuries, and sometimes after so trifling lesions as those inflicted by dirty pointed instruments, or even the stings of insects.

The characteristic feature of the disease is the rapidity of its spread, the septic character of the inflammatory product, and the speedy destruction of the tissue involved, with the formation of gas. A dirty brownish, reddish skin, mottled with blue, whose veins are filled with stagnant blood, covers the affected areas. The underlying tissues are sodden with fluid and distended with gaseous products of decomposition. so that the finger feels a fine crepitus, as is common in subcutaneous emphysema. From the wound, if there be one, flows a thin, foul smelling secretion, which may also be expressed from the deeper layers. That the neighboring lymph spaces, vessels and glands are actively participating in the transmission of septic products is evident from the enormous swelling which the latter present, and from the general condition of the patient. The rapid elevation of temperature, with but trifling remission, remains constant until shortly before death. The tongue early becomes dry, cleaves to the palate, its surface covered with thick foul fur. Consciousness is early lost and patients become peculiarly apathetic, complaining only of pain and burning thirst. Sometimes they are delirious instead of apathetic; coma, incontinence, frequent and superficial breathing and dilatation of the pupil are the precursors of death, which may occur in from fifteen to thirty hours. In rare cases life has been saved by the introduction of most vigorous stimulants and sustaining measures. After death the cadaver bloats quickly and putrefaction goes on with singular rapidity. At the seat of the lesion muscles and tendons will be found macerated, the bone denuded, surrounded by a putrid fluid, and the entire region presenting a notable swelling and infiltration of the soft parts with reddish fluid and stinking gases. It is in this fluid that one finds the largest number of micro-organisms. The overlying skin will be stretched and superficial blebs or blisters may typify the intensity of the process. The water-logged muscles are friable, the veins are engorged with black and decomposed blood and broken down thrombi, and in the heart and large vessels will be found at the same time putrid liquid and gas, to the presence of which latter the early and sudden death has been with much propriety attributed, since it may cause death in the same way as does air embolism. The viscera are congested and œdematous, and present hæmorrhagic infarcts.

This terrible complication supervenes ordinarily within from eight hours to six days after injury. Its approach has been sometimes betokened by depression and sadness and by chills. Frequently excessive pain and sense of constriction are complained of around the wound. Sometimes the skin has assumed such a peculiar appearance as to justify the term bronze erysipelas, given it by Velpeau (*érysipèle bronze*). The gaseous products of putrefaction, crepitating under the finger, rapidly infiltrate the wound, distend the cellular tissue and extend along the vessels to the glands. The injured spot instead of suppurating simply dies and emits an abundant sanious liquid.

It remained for Koch, in 1882, to demonstrate upon the smaller animals a pathogenic bacillus which he had recognized and cultivated, and which also Pasteur had described under the name *vibrion septique*. This organism is a bacillus much resembling in form and size that of anthrax. Nevertheless it has certain important points of difference by which it can be easily recognized. It is somewhat smaller than the bacillus of anthrax, has rounded ends, and is joined in threads after a fashion quite different. It possesses the property of spontaneous motion, which anthrax bacilli do not possess. The most important morphological difference, however, is in spore formation, since when these bacilli produce spores they enlarge in the middle or at one end, in which enlargement the oval, brilliant and bluish spore is soon developed. Bacilli of malignant œdema take stains just about as do those of anthrax, but they evince much less resistance to Gram's method than do the others; it is in cultures that they show the widest differences.

They do not grow on gelatine plates after the common fashion nor even in needle cultures except when the needle is driven down deeply, almost to the bottom of the gelatine tube, and then they grow along the lower portion of the needle track. Thus it will be seen that these bacilli belong to the most marked form of anærobic organisms with which we are acquainted, and that they grow only when oxygen is entirely excluded. Pasteur was the first to succeed in cultivating them in this medium with the exclusion of air. Gaffky invented a method of cultivation by introducing into the interior of a cooked potato a fragment of tissue in which they were growing. Hesse later taught how to make pure cultures of them in agar and gelatine, by simply sinking fragments of infected tissue into the depths of the tubes, while Flugge, by resorting to cultures in vacuo, succeeded in attaining the same object.

The bacilli of malignant œdema grow best in nutrient gelatine to which 1 or 2% of grape sugar has been added. In such a medium the needle streak shows the development of the organisms at first in its lowermost portion by a series of minute varicosities, which consist in the interior of opaque fluidified gelatine, and around the margin of fine radiating streaks. In their further course the entire lowermost portion of the gelatine liquifies and becomes opaque. In agar they behave in much the same way, save that they do not fluidify the medium. The minute chemistry of these changes is not known. It can hardly be considered a putrefaction since no foul-smelling product is produced. On agar plates where they can be grown in an atmosphere of hydrogen the colonies show very distinctly. Coagulated blood serum is quickly fluidified by them with production of gas. In all media they grow best at body temperature, although even at 18° or 20°C. they show a typical proliferation. According to most authors spores are never formed in the living body, spore formation being apparently a post-mortem phenomenon.

In most respects these bacilli behave as out-spoken saprophytes. Their known habitat is, in fact, the outer world, from which do they only rarely make an incursion into the animal body. They are most commonly met with in the outermost layers of the soil, and garden earth nearly always contains them. Aside from this they may be met with in any kind of soil or dust. The researches of Gaffky seem to make it clear that the bacilli may penetrate from the intestinal canal into the body tissues. The horse seems to manifest the greatest predisposition for the disease, although it may be met with or artificially produced in all domestic animals. A few years ago Brieger and Ehrlich reported an extremely interesting case of malignant œdema following typhoid fever, in which the disease followed a clinically typical course to its fatal termination. Rosenbach later reported two typical cases not connected with typhoid, in which he found the bacilli in question. We must not omit in this place, however, to mention that gangrenous emphysema, more or less resembling the disease under consideration, may be produced by other bacteria, especially the more ordinary putrefactive forms, and that the necrosis or gangrene proper, which is so significant a part of the picture in malignant œdema, is not primarily produced by the specific bacilli, as may be proven by the results of experiment. When a pure culture of these specific bacilli is injected, there is produced a most extensive hæmorrhagic œdema of the subcutaneous cellular tissue without any appearance of putrefactive action; and quite free from gas formation; but when an impure culture is injected, or when garden earth is used for in-inoculation, the distinctive œdema of the previous instance becomes a mixture of emphysemic œdema and gangrene, which latter is, in all probability, due to a mixed infection of the common putrefactive forms, among which, perhaps, may be reckoned the pseudo-œdema bacillus of Liborius.

Experiments on animals seem to indicate that an ordinary cutaneous inoculation is of no effect, nor even is an intra-veinous infection of the organisms. They need to be planted subcutaneously in the areolar tissues in order to produce the typical results. Those which are injected into the blood probably find in the arterial capillaries too much oxygen to permit of their living. The fact that they do not enter through a mere abrasion of the skin is probably the secret of the known immunity of man and beast from this disease, since the earth in which laborers work day after day with abraided hands and feet, and yet with impunity, is the same as that which, introduced beneath the skin of a guinea pig, will quickly determine its death. Nevertheless, the disease is not always fatal, and the larger animals not infrequently recover. Microscopical examination of the tissues from an infected area, supposing the examination to have been made immediately after death, shows that the bacilli are never found inside of the blood-vessels, but mainly in the superficial tissues of the thorax and abdomen, or possibly in the lymphatic spaces of the pleura or of the peritoneum. The blood and tissues of the mouse constitute a possible exception to the above statement. According to certain French investigatiors one attack of this disease confers immunity from subsequent infection, but the opposite view has been taken by others, that one invasion of the disease leaves the system particularly susceptible to others.

Last summer a case was related to me by a Russian physician, Dr. Rekowski, of malignant œdema apparently the result of a hypodermic injection of a solution of morphine. At that time the Doctor was investigating this subject in the laboratory of the Hygienic Institute in Berlin. I have not yet seen any publication of his results, although I know he intended to ascertain the effect of morphia in solution as accelerating or inhibiting the growth of these organisms. At all events such a case as this adds this possible danger to the already formidable list of dangers from injections of solutions not freshly made.

Quite recently Roger has made some very interesting experiments with the bacillus of malignant œdema, and has shown that rabbits possess refractory organisms, but if he introduced at the same time virulent œdema bacilli along with the bacillus prodigiosus, there developed the most characteristic features of œdema, and the animals died inside of twenty-four hours. The œdema bacilli could be recognized in the blood and in the internal organs, the other variety only at the point of inoculation. The œdema bacilli from the first animal were now able to kill the second when inoculated, but when the third was inoculated from the second there was no result. These experiments are convincing that microbes which are not pathogenic for a certain species of animal can be made so when inoculated together with others.

RAUSCHBRAND.

Rauschbrand is a disease quite common among cattle in central Europe, known to the French as *charbon symptomatique*, and to the Italians as *carbonchio sintomatico*, while in Great Britain it is called the *black-leg*. It is a disease very similar in its manifestations to malignant œdema, is well known to be due to an anærobic bacillus, and has so much in common with malignant œdema that I have proposed to speak of it for a moment here, although I have been unable to find in literature any case in which a human being has been attacked with it. A most marked difference between the two forms of trouble is the formation of gas in the diseased tissue, which in the case of malignant œdema is of putrefactive odor; otherwise it might be hard to tell sometimes with which condition we have to deal.

The bacilli of rauschbrand possess many similarities to those of malignant œdema. In form and size there is of course a resemblance, but with minute differences in the manner of spore formation; while the rauschbrand bacilli seem to be in the highest degree anærobic. In their manner of growth there are also trifling yet distinctive differences, and it is found that inside of living tissue spore formation, which apparently takes place only at the end of each organism, occurs with greater freedom. They are also more motile than those of malignant œdema. The most notable differences are observed in different animals in their liability to the two diseases. Cattle are apparently the proper victims of rauschbrand, while they are not subject to malignant œdema. On the other hand swine, dogs, rabbits, fowls and pigeons are but little, if at all, subject to rauschbrand, but succumb very readily to œdema. Horses can be made to react upon artificial inoculation, but appear never to suffer from spontaneous rauschbrand. They are ready victims to the bacilli of malignant œdema. Another significant difference between the organisms is their common habitat. Oedema bacilli seem to be found everywhere in the more superficial layers of earth, whereas rauschbrand seems to be strictly confined to certain localities, although what it is that brings about this state of affairs is not yet known. Again, survival from one attack of rauschbrand, or vaccination with attenuated virus, seems to confer immunity, whereas this is not the case with malignant œdema, but rather there seems to remain an increased susceptibility to the disease.

It was, indeed, a recognition of the former fact, namely, the immunity which one attach of rauschbrand confers, that led Arloing and his co-workers to practice protective inoculation, which now has been very extensively carried out; and it seems to have served a most excellent and useful purpose. It seems to be the general conclusion that rauschbrand bacilli are capable of transmission from mother to fœtus, and that the latter may be affected in this way. The positive proof of this fact which has apparently been furnished is of wide reaching importance, because if it can occur with one organism, it can undoubtedly with others, and this is a principle which needs to be well established because of its important bearing upon the question of transmission of disease. Within the past year or two there has been apparently a large amount of interest excited in these questions, and a number of workers have devoted a large amount of time and energy to the work, especially in estimating the absolute protective value of preventive inoculation as against this disease, as also in putting an estimate of the money value and giving the whole matter an aspect of national financial importance. The outcome of this work appears to indicate that preventive vaccination offers nearly the same protection against rauschbrand that in another way it offers against small-pox in the human race.

Roger has studied the immunity of rabbits against rauschbrand. It is possible to increase their natural immunity by injecting into their veins daily a number of rauschbrand bacilli. If, after this, rauschbrand bacilli and b. prodigiosus mixed together are injected into the muscles, then the animal shows at most some reaction, from which it soon recovers. Whereas were not the specific bacilli first injected in the veins they would always perish.

From a series of experiments of this kind, suitably varied, Roger comes to the conclusion that the chemical products of the b. prodigiosus do not, as he had at first supposed, alter the tissue at the point of inoculation, but that they act on the entire organism. He obtained the same results with pigeons, which, like rabbits, are refractory to the disease. The susceptibility of rabbits to this disease after the injection of the prodigiosus does not remain long, and they soon become refractory again. He found further that rabbits, which were not affected by intramuscular injection of rauschbrand bacilli, developed the disease when the same were injected into the anterior chamber. From this they died in eighteen to forty hours. The eye is swollen and often contains gas. The entire organ becomes sodden with bloody fluid in which bacilli abound. A similar exudate occurs at the base of the brain. If he injected rabbits in both ways at the same time, *i. e.*, in the anterior chamber and the muscles of the thigh, then rauschbrand bacilli were found also at the latter point. A sterilized infusion of muscles thus affected, injected into another rabbit, produced somnolence. If, at the same time, the injected animal were also inoculated with virulent rauschbrand it quickly died; but if the inoculation were postponed twenty-four hours it became in the mean time insusceptible.

FARCY: GLANDERS.

Various authors have described from a clinical point of view four varieties of this infectious malady, which have been described under the terms acute and chronic farcy and acute and chronic glanders; under the former term grouping those varieties in which the superficial tissues are the more affected, and under the latter those in which the deeper cavities, like the nasal fossæ, the lungs, and the deeper glands, are affected. To-day, however, these descriptions have much less importance, since we recognize the same infectious agent active in them all, and we know that by means of a lymphangitis extending from a farcy bud, we may be led to find a deep abscess, and that the deep ulcerations in the complicated cavities of the skull differ in no essential respect from those upon the skin.

Some of the difficulties of diagnosis in some of these cases may be gathered from such a case as the following which Bucquoy reported to the French Academy of Medicine in 1883: A young man, æt. 19, of alcoholic habits, and suffering from recent syphilis, was admitted into the hospital, displaying upon one leg a fungus ulcer as to whose origin he was entirely ignorant; and upon the thigh of the same side was a small fluctuating swelling of livid hue, quite like abscesses which one observes after contusions; his general condition seemed to be that of typhoid fever. On the fourteenth day after admission there appeared on each side of the ankle a phlegmonous swelling with redness and œdema; on account of this arthritis the diagnosis of typhoid was discarded and the case was regarded throughout as one of some septic or purulent infection. His condition became more serious; four days later he was delirious and other joints became involved after the same fashion, while the synovial cavities were distended with fluid; the abscess about the ankle was opened and considerable pus evacuated. On the following day he was unconscious, and a peculiar bullous eruption appeared all over the body. On account of this eruption the specific infection of glanders was suspected, although there were no nasal symptoms. He died twenty-two days after admission. The liver contained a large abscess and many of the joints contained pus. The true character of the disease was established by careful inquiry into his antecedents, which showed that he had come in contact with horses suffering with glanders, and by the results of inoculation of some of the fluids upon animals. An ass inoculated with some of this material developed a very typical swelling of the sub-maxillary glands, and died ten days after vaccination.

We do not at present recall any other case where the diagnosis was established or verified by such inoculation.

The specific organism of glanders, known as the *bacillus mallei*, has perhaps been the most carefully studied by Löffler. It is a little shorter and broader than the tubercle bacillus, varying but little in length. Commonly they are found in pairs side by side, often held together by a little hyaline material which takes no stain. In fluid media they show active molecular motion, but no spontaneous motility. The organism is peculiar in this respect, that by no means all of the bacilli form spores, and spore formation seems to occur only at times, upon the favorable surroundings. Reaction to staining media is peculiar, since these bacilli take no basic aniline dyes. They grow best on blood serum and potato, but may be cultivated in other media. They show about the same degree of resistance to heat and chemicals as other nonspore-bearing bacilli —are destroyed by exposure for ten minutes to a temperature of 55° C. The animals which are most susceptible are the horse, cow, sheep, guinea-pig, rabbit, white rat, cat, tiger and lion; while common pigs, dogs, the common rat and domestic fowl enjoy great immunity.